PCT / SE 2005 / 000238

22 -02- 2005

REC'D 04 MAR 2005

WIPO PCT

PA 1280682

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 07, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/549,225***
FILING DATE: ***March 01, 2004***

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. Jackson

H. L. JACKSON
Certifying Officer

PTO/SB/16 (08-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 116913666 US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Ola	CARLSSON	Lund, Sweden

Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

A MEDICAL SOLUTION, A METHOD FOR PRODUCING SAID MEDICAL SOLUTION AND USE THEREOF

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☑ Customer Number: 24994

OR

☐ Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 40
☑ Drawing(s) *Number of Sheets* 6
☐ Application Date Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.
☐ A check or money order is enclosed to cover the filing fees.
☑ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 032316
☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): 160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE Laura M. Butterfield

Date 03-01-2004

TYPED or PRINTED NAME Laura M. Butterfield

REGISTRATION NO. 47466 *(if appropriate)*

Docket Number: N0383-US01

TELEPHONE 303-231-4270

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PROVISIONAL APPLICATION COVER SHEET
Additional Page

PTO/SB/16 (08-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Docket Number N0383-US01

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Martin	ERIXON	Malmö, Sweden
Torbjörn	LINDÉN	Linderöd, Sweden
Gunita	FORSBÄCK	Linderöd, Sweden
Per	KJELLSTRAND	Södra Sandby, Sweden
Anders	WIESLANDER	Lund, Sweden

Number 2 of 2

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Docket No. **N0383-US01**

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

In re Application of: **CARLSSON, Ola et al**
Serial No.: **To be assigned**
Filed: **Herewith**
For: **A Medical Solution, A Method for Producing Said Medical Solution and Use Thereof**
Customer Number: **24994**

Group Art No: **To be assigned**
Examiner: **To be assigned**

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)

I hereby certify that the following documents:

1. **Certificate of Express Mailing (1 pg)**
2. **Provisional Application for Patent Cover Sheet (2 pgs)**
3. **Specification (40 pgs)**
4. **Drawings (6 sheets)**
5. **Return Card**

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to:

Mail Stop Provisional - Patent Application
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

on this date of 03/01/2004

Yanmin Huang

EV 116913666 US
Express Mailing Label Number

A MEDICAL SOLUTION, A METHOD FOR PRODUCING SAID MEDICAL SOLUTION AND USE THEREOF

Technical field of the present invention

The present invention relates to a medical solution comprising a first single solution containing glucose and/or glucose-like compounds, a method for producing said medical solution as well as use thereof.

Background of the invention

Many medical solutions contain glucose and/or glucose-like compounds in different amounts are known. It is also known that glucose and/or glucose-like compounds give rise to problems during sterilization of medical solutions, see for example "Toxicity of peritoneal dialysis fluids on cultured fibroblasts L-929" by Anders Wieslander et al, Kidney International , Vol 40 (1991) pp 77-79.

During sterilization adding energy and/or during storage of solutions containing glucose and/or glucose-like compounds harmful components are formed. These components are formed by decomposition glucose and/or glucose-like compounds and are referred to as Glucose Degradation Products (GDPs).

During long-term peritoneal dialysis several problems arise as a consequence of the presence of GDPs in the Peritoneal Dialysis fluids (PD fluids).

Accordingly, new PD fluids have been developed with the aim to reduce the amount of GDPs.

The focused problem so far has been to reduce/minimize the total amount of GDPs in different solutions in order to keep the solution as biocompatible as possible.

The main part of these GDPs are however still unknown making the choice of a suitable marker for the reduction problematic.

One object of the present invention is thus to specifically optimize a medical solution in regard to biological reactivity and not only on the total amount of GDPs.

Summary of the invention

The present invention relates to a medical solution comprising a first single solution containing glucose and/or glucose-like compound. According to the present invention said first single solution has a pH in the range of 1.8-2.6. The present invention further relates to a method for producing said medical solution as well as use thereof.

The inventors of the present invention have identified a new, highly reactive GDP named 3,4-dideoxy-glucosone-3-ene (3,4-DGE), which has shown to be strongly connected to the cytotoxicity of PD fluids.

The present inventors have in several experiments found a good dose relation between 3,4-DGE and cytotoxicity, see fig 1.

Thus for the first time a medical fluid containing glucose and/or glucose-like compounds could be optimized with a clear and relevant focus, which is, minimizing the concentration of the highly toxic 3,4-DGE.

One advantage of the present invention is that it provides a medical solution having extremely low concentration of toxic 3,4-DGE.

Applied in Peritoneal Dialysis this medical solution likely preserve the peritoneal membrane of the patients during long-term dialysis.

In a preferred embodiment of the invention the pH of the first single solution is at least 1.8, preferably at least 2.0 and at most 2.6, preferably at most 2.5, most preferably at most 2.3.

In another preferred embodiment of the invention said medical solution further comprise a second single solution. This second single solution contains a buffer solution having such a pH and buffering capacity that when said first and second single solutions, up on use, are mixed to form a final solution, said final solution has a pH of 6.0-7.6.

In another preferred embodiment of the invention, said medical solution further contains one or more electrolytes, and the one or more electrolytes are preferably chosen from the group comprising ions of sodium, calcium, potassium, magnesium and/or chloride. Said one or more electrolytes is in one preferred embodiment arranged in said second single solution, but could also totally or to some extent be arranged in said first single solution.

In another preferred embodiment of the invention said medical solution further comprise a third single solution. Said third single solution also contains glucose and/or glucose-like compounds and has a pH of at least 1.8, preferably at least 2.0 and a pH of at most 2.6, preferably at most 2.5, most preferably at most 2.3. Said optional one or more electrolytes could also totally or to some extent be arranged in said third single solution.

In another preferred embodiment of the present invention said first and third single solutions contain different total amounts of glucose and/or glucose-like compounds. Up on use, said first or third single

solution, individually or jointly is/are to be mixed with said second single solution to form a final solution. Said final solution has a pH in the range of 6.0-7.6.

According to one preferred embodiment of the invention, the different single solutions are provided in different compartments in a multicompartment bag before being mixed to the final solution.

As stated above the present invention also relates to a method for producing said medical solution. According to the method, said first single solution and optional second and third single solutions are provided in separate compartments. Thereafter said single solution(s) is(are) terminally sterilized.

In a preferred embodiment of the method according to the invention said terminal sterilization is heat sterilization and/or radiation sterilization. In another preferred embodiment of the invention, said terminal sterilization is heat sterilization at a temperature of at least 100°C, preferably at least 121°C.

In another embodiment of the method according to the present invention said first single solution and said second single solution, after terminal sterilization and up on use, are mixed to form a final solution.

In another embodiment of the method according to the present invention said second single solution and said third single solution, after terminal sterilization and up on use, are mixed to form a final solution.

In another embodiment of the method according to the present invention said first, second and third single solutions, after terminal sterilization and up on use, are mixed to form a final solution.

The present invention further relates to a multi-compartment bag comprising the medical solution according to above.

The present invention also relates to the use of the medical solution as disclosed above.

Additional objects, features, advantages and preferred embodiments of the present invention will become apparent from the following detailed description when taken in conjunction with the enclosed claims.

Definitions

The term "medical solution" is intended to mean dialysis solutions for peritoneal dialysis, hemodialysis, hemodiafiltration, hemofiltration, for dialysis within renal intensive care, solutions for substitution or infusion normally containing glucose and/or glucose-like substances, and solutions for nutrition purposes.

The term "single solution" is intended to mean one solution kept isolated from other solutions up until use. The different single solutions could be used alone or mixed together with one or more single solutions up on use. Preferably, at least two single solutions are to be mixed up on use.

The term "glucose and/or glucose-like compound" is intended to mean compounds giving rise to glucose- or glucose polymer-derived toxins.

The term "buffer solution" is intended to mean solutions having a pH buffering capability to buffer the final solution into a pH range of 6.0-7.6.

The term "final solution" is intended to mean the solution which is ready to use and includes the required combination of different single solutions.

The term "electrolytes" is intended to mean the ions essential for the intended medical solution.

The term "multicompartment bag" is a bag divided into more than one compartment and that the content in the different compartment could be brought together and mixed before use.

The term "terminal sterilization" is intended to mean that the product is sterilized in its final package. The terminal sterilization may include heat sterilization and/or radiation sterilization, but is preferably heat sterilization effected in an autoclave at a temperature of at least 100°C, preferably at least 121°C.

The term "up on use" is intended to mean as close as possible before the medical solution is used for it´s specific purpose.

Brief description of the drawings

Fig. 1 is a diagram showing the relation ship between Inhibition of Cell Growth (ICG) and concentration of 3,4-DGE in a solution.

Fig. 2a is a diagram showing the results of different pH on 5-HMF measured at 0, 6 and 30 days (series 1, 2 and 3, respectively) after heat sterilization.

Fig. 2b is a diagram showing the results of different pH on 3-DG measured at 0, 6 and 30 days (series 1, 2 and 3, respectively) after heat sterilization.

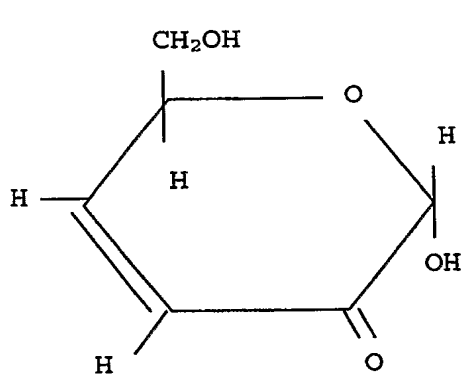
Fig. 2c is a diagram showing the results of different pH on 3,4-DGE measured at 0, 6 and 30 days (series 1, 2 and 3, respectively) after heat sterilization.

Fig. 3 is a diagram showing the relative amounts of the 5-HMF, 3-DG and 3,4-DGE, respectively at different pH values after 30 days of incubation.

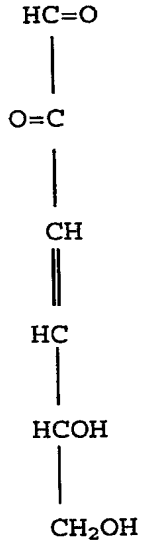
Fig. 4 is a diagram showing the sum of the 5-HMF, 3-DG and 3,4-DGE concentrations at different pH values after 30 days of incubation.

Detailed description of the invention

The highly toxic GDP, 3,4-DGE, has the two following cis and trans formulas:



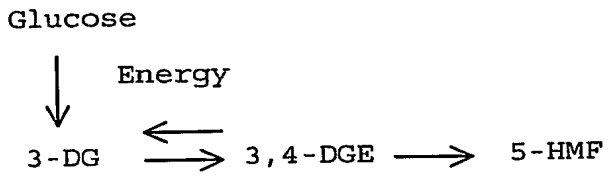
cis



trans

Other GDPs are for example acetaldehyde, formaldehyde, glyoxal, methylglyoxal, 3-deoxyglucosone (3-DG), 5-hydroxymethylfuraldehyd (5-HMF).

When glucose is exposed to sterilization adding energy, the following reaction takes place:



As shown above, 3-DG is in equilibrium with 3,4-DGE and 3,4-DGE is further transformed over to 5-HMF.

Extensive work has been done to optimize a medical solution containing glucose and/or glucose-like compounds in order to minimize the toxicity thereof.

In order to investigate and come up with the present invention, the present inventors studied the relationship between the different GDPs and came to the conclusion that the GDPs interact according to the reaction formula given above. Further, the inventors investigated and found that 3,4-DGE is the most toxic of the known GDPs and that there is a dose dependent relationship between the concentration of 3,4-DGE and the Inhibition of Cell Growth (ICG) used as a measure/marker for biological reactivity, see the enclosed figure 1.

Due to the correlation between 3-DG, 3,4-DGE and 5-HMF, the inventors chose to investigate the generated amounts of these GPDs in different solutions at different pH and after different storage time.

Solutions containing 50 % by weight of glucose with different pH within the range of 1-4 were prepared. The different solutions were exposed for sterilization in form of heat sterilization in an autoclave at a temperature of 121°C during 40 min.

The concentrations of 5-HMF, 3-DG and 3,4-DGE were measured after 0 days (serie 1), 6 days (serie 2) and 30 days (serie 3) after sterilization. During storage before the measurements at day 6 and 30, respectively, the solutions were kept at 40°C to reflect the "worst storage scenario" possible.

The results are shown in Fig. 2a-c for 5-HMF, 3-DG and 3,4-DGE, respectively.

To be able to investigate the pH area which is the most optimal, the different results were put together in one diagram. To be able to weight the different GDPs after 30 days of storage in a correct way, the % of maximum concentration was plotted towards pH value. See Fig. 3 for the resulting diagram.

In figure 4 the sum of 3,4-DGE, 3-DG and 5 HMF concentrations after 30 days of storage has been ploted as a function of pH. It is, however, important to note that 3,4-DGE and 3-DG concentrations is more important than 5-HMF for the toxicity and a slight increase in the sum of the measured GDPs can be accepted in the lower range.

In the decision on how to choose the best pH range for the medical solution, it is not only important to keep the 3,4-DGE as low as possible. It is also important to look into the dynamics of the reaction formula for GDPs, as the reaction is an equlibrium between 3-DG and 3,4-DGE, while 5-HMF is an end product. This means that the 3-DG always could be changed into 3,4-DGE and vice versa. 5-HMF, on the other hand, is an end product, and after having been degraded to 5-HMF, there is no return to the most toxic GDP, namely, 3,4-DGE.

Knowing this, one quick solution to the problem seems to be to process the solution in such a way that

all GDPs are reacted towards 5-HMF. However, 5-HMF still is a GDP and this GDP can participate in different polymerisation reactions and turn the medical solution yellow. It may possible cause not yet observed/described side-effects for the patient.

Accordingly, it is important to take all GDPs into consideration before deciding on the solution as such, and this is what the inventors of the present invention have done, and they have come up with the medical solution according to the claimed invention.

The medical solution according to the invention comprises a first single solution containing glucose and/or glucose-like compounds. This first single solution has a pH of at least 1.8, preferably at least 2.0 and a pH of at most 2.6, preferably at most 2.5, most preferably at most 2.3.

In one preferred embodiment the first single solution has a pH in the range of 1.8-2.6. In another preferred embodiment of the invention the first single solution has a pH in the range of 2.0-2.6. In another preferred embodiment of the invention the first single solution has a pH in the range of 1.8-2.5, and in even another preferred embodiment of the invention the first single solution has a pH in the range of 2.0-2.5.

In another preferred embodiment of the invention the first single solution has a pH in the range of 1.8-2.3, and in even another preferred embodiment of the invention the first single solution has a pH in the range of 2.0-2.3.

Besides optimizing the pH of the first single solution, the concentration of the glucose and/or glucose-like compounds also have an input, however, pH has the largest impact on the amount of produced GDPs.

Preferred concentrations of glucose and/or glucose-like compounds in said first single solution is at least 10 % by weight, preferably at least 20 % by weight, and most preferably at least 40 % by weight, based on the total weight of the first single solution.

In a preferred embodiment of the present invention the medical solution comprises a second single solution containing a buffer solution having such a pH and buffering capacity that when said first and second single solutions, up on use, are to be mixed to form a final solution, said final solution has a pH within the range of 6.0-7.6.

Preferably, the buffer solution comprises at least one of the following; bicarbonate, carbonate, acetate and lactate or combinations thereof.

If bicarbonate and/or carbonate is use either alone or in combination with any of the other suggested substances with buffering capability, a combination of bicarbonate and carbonate preferably is provided in such proportions that the partial pressure of carbon dioxide, CO_2, in the second single solution is of the same order of magnitude as the partial pressure of carbon dioxide, CO_2, in the atmosphere.

Using this buffer of a combination of bicarbonate and carbonate, an additional single solution comprising an acid and having a pH of 1.0-1.5, preferably 1.3 also is included. The second single solution comprising this combination of bicarbonate and carbonate preferably has a pH of 10.1-10.5, preferably 10.3. In this case said second single solution together with the additional single solution constitute the buffer solution.

In a preferred embodiment of the present invention the medical solution comprises a third single solution.

This third single solution has the same preferred features as said first single solution.

In the preferred embodiment of the present invention the medical solution with said first, second and third single solution, said first and third single solutions could, according to a preferred embodiment of the invention, comprise different total amounts of glucose and/or glucose-like compounds. The different total amounts could be achieved by providing the same concentrations within said first and third single solutions, but providing different volumes thereof. The different total amounts could also be achieved by providing the same volume of said first and third single solutions, but providing different concentrations in said first single solution in comparison with said third single solution.

Having a preferred medical solution comprising said first, second and third single solutions, the user thereof could choose what concentration of glucose the user would like to have for a specific treatment. By combining said first and second single solutions to a final solution, the user gets a first specific concentration of glucose and/or glucose-like compounds, by combining said third and second single solutions to a final solution, the user gets a second specific concentration of glucose and/or glucose-like compounds, and by combining said first, second and third single solutions to a final solution, the user gets a third specific concentration of glucose and/or glucose-like compounds.

Accordingly, said first and third single solutions could, up on use, be mixed individually, i.e. either first or third single solution together with said second

single solution, or joinly, i.e. both first and third single solutions together with said second single solution to form a final solution. Note that said final solution always have a pH within the range of 6.0-7.6, no matter which of the combinations above are used. The buffer solution in said second single solution have the capability to buffer said first and/or third solution(s) to a pH of 6.0-7.6 in the final solution.

Said single solutions could be provided in different compartments in a multi-compartment bag, and the mixing could be provided by having the different compartments sealingly coupled by frangible pins, which different pins could be broken in order to mix the content in optional compartments within the multicompartment bag. The mixing could further be provided by having a peal seal in between the different compartments, which peal seal could be pealed in order to mix the content in the different compartments. Two examples of multi-compartment bags are shown in figs. 5 and 6.

In another preferred embodiment of the invention the medical solution further contains one or more electrolytes. Preferably, the electolytes is one or more of the ions of sodium, calcium, potassium, magnesium and chloride.

The arrangement of electrolytes in the different compartments is dependent on the different electrolytes co-behavior with the other substances present in the single solutions, i.e. whether some sort of reaction could occur between the electrolyte(s) and the other substances present in a specific single solution(s). Usually, the electrolytes are contained in said second single solution. However, if bicarbonate is used as a buffer solution, the calcium ions preferably is provided

in said first or third single solution. The reason for this is that calcium and bicarbonate together could cause precipition of calcium carbonate. However, calcium ions could be kept with bicarbonate under certain circumstances, such as in a specific pH range. This is for example disclosed in EP 0 437 274, which hereby is enclosed by reference.

In the method for producing the medical solution according to above, said first single solution and optional second and third single solutions are provided in separate compartments. Thereafter said single solution(s) is(are) terminally sterilized. Preferably the terminal sterilization is heat sterilization and/or radiation sterilization, (see also European Pharmacopoeia 1977 for a review of different sterilization techniques). In a preferred embodiment of the method according to the invention, the terminal sterilization is heat sterilization at a temperature of at least 100°C, preferably at least 121°C.

The sterilization time may vary depending on the sterilization temperature, the type of container and the contents therein to be sterilized.

The radiation sterilization may be either ionising or non-ionising sterilization. Examples of ionising sterilization are gamma and beta radiation. Example of non-ionizing radiation sterilization are UV radiation.

The medical solution according to the present invention has the advantage of having extremely low concentrations of the most toxic GDP, namely 3,4-DGE, and when used as a peritoneal dialysis solution it is likely to preserve the peritoneal membrane of the patients during long-term dialysis.

Below you will find different examples of solutions according to the present invention.

Exampels

By way of example, and not limitation, the following examples identify a variety of solutions made pursuant to an embodiment of the present invention.

Example 1-3

Three-compartment bag with lactate

Compartment 1 (first single solution):

	Example 1	Example 2	Example 3
Volume (l)	0,062	0,062	0,062
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 2 (third single solution):

	Example 1	Example 2	Example 3
Volume (l)	0,103	0,103	0,103
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 3 (second single solution):

	Example 1	Example 2	Example 3
Volume (l)	1,96	1,96	1,96
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	54,2	54,2	54,2
Lactate (mM)	42,11	42,11	42,11
Ca^{2+} (mM)	1,84	1,84	1,84
Mg^{2+} (mM)	0,27	0,27	0,27

Solution, mixed and ready for use:

Example 1	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Lactate (mM)	40,8	40,0	38,8
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 2	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Lactate (mM)	40,8	40,0	38,8
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

5

Example 3	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Lactate (mM)	40,8	40,0	38,8
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 4-6

Three-compartment bag with acetate

Compartment 1 (first single solution):

	Example 4	Example 5	Example 6
Volume (l)	0,062	0,062	0,062
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 2 (third single solution):

	Example 4	Example 5	Example 6
Volume (l)	0,103	0,103	0,103
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 3 (second single solution):

	Example 4	Example 5	Example 6
Volume (l)	1,96	1,96	1,96
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	54,2	54,2	54,2
Acetate (mM)	42,11	42,11	42,11
Ca^{2+} (mM)	1,84	1,84	1,84
Mg^{2+} (mM)	0,27	0,27	0,27

Solution, mixed and ready for use:

Example 4	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	40,8	40,0	38,8
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 5	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	40,8	40,0	38,8
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 6	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	40,8	40,0	38,8
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 7-9

Three-compartment bag with lactate + acetate

Compartment 1 (first single solution):

	Example 7	Example 8	Example 9
Volume (l)	0,062	0,062	0,062
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 2 (third single solution):

	Example 7	Example 8	Example 9
Volume (l)	0,103	0,103	0,103
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 3 (second single solution):

	Example 7	Example 8	Example 9
Volume (l)	1,96	1,96	1,96
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	54,2	54,2	54,2
Acetate (mM)	12,11	12,11	12,11
Lactate (mM)	30,0	30,0	30,0
Mg^{2+} (mM)	1,84	1,84	1,84
Ca^{2+} (mM)	0,27	0,27	0,27

Solution, mixed and ready for use:

Example 7	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	11,7	11,5	11,2
Lactate (mM)	29,1	28,5	27,7
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 8	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	11,7	11,5	11,2
Lactate (mM)	29,1	28,5	27,7
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

5

Example 9	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	11,7	11,5	11,2
Lactate (mM)	29,1	28,5	27,7
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Examples 10-12

Three-compartment bag with lactate + bicarbonate

Compartment 1 (first single solution):

	Example 10	Example 11	Example 12
Volume (l)	0,062	0,062	0,062
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 2 (third single solution):

	Example 10	Example 11	Example 12
Volume (l)	0,103	0,103	0,103
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 3 (second single solution):

	Example 10	Example 11	Example 12
Volume (l)	1,96	1,96	1,96
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	54,2	54,2	96,28
Bicarbonate (mM)	12,11	12,11	12,11
Lactate (mM)	30,0	30,0	30,0
Mg^{2+} (mM)	1,84	1,84	1,84
Ca^{2+} (mM)	0,27	0,27	0,27

Solution, mixed and ready for use:

Example 11	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Bicarbonate (mM)	11,7	11,5	11,2
Lactate (mM)	29,1	28,5	27,7
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 11	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Bicarbonate (mM)	11,7	11,5	11,2
Lactate (mM)	29,1	28,5	27,7
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 12	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Bicarbonate (mM)	11,7	11,5	11,2
Lactate (mM)	29,1	28,5	27,7
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 13-15

Three-compartment bag with acetate + bicarbonate

Compartment 1 (first single solution):

	Example 13	Example 14	Example 15
Volume (l)	0,062	0,062	0,062
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 2 (third single solution):

	Example 13	Example 14	Example 15
Volume (l)	0,103	0,103	0,103
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 3 (second single solution):

	Example 13	Example 14	Example 15
Volume (l)	1,96	1,96	1,96
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	54,2	54,2	54,2
Acetate (mM)	30,0	30,0	30,0
Bicarbonate (mM)	12,11	12,11	12,11
Mg^{2+} (mM)	1,84	1,84	1,84
Ca^{2+} (mM)	0,27	0,27	0,27

Solution, mixed and ready for use:

Example 13	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	29,1	28,5	27,7
Bicarbonate (mM)	11,7	11,5	11,2
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 14	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	29,1	28,5	27,7
Bicarbonate (mM)	11,7	11,5	11,2
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 15	1+3	2+3	1+2+3
Volume (l)	2,022	2,063	2,125
Glucose (g/l)	15,33	24,96	38,82
Na^+ (mM)	132,9	132,1	130,9
Cl^- (mM)	55,3	56,1	57,1
Acetate (mM)	29,1	28,5	27,7
Bicarbonate (mM)	11,7	11,5	11,2
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,79	1,75	1,70

Example 16-18

Two-compartment bag with lactate, 2,5 % glucose

Compartment 1 (first single solution):

	Example 16	Example 17	Example 18
Volume (l)	0,100	0,100	0,100
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 2 (second single solution):

	Example 16	Example 17	Example 18
Volume (l)	1,9	1,9	1,9
Na^+ (mM)	134,1	134,1	134,1
Cl^- (mM)	91,4	91,4	91,4
Lactate (mM)	42,11	42,11	42,11
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,84	1,84	1,84

Solution, mixed and ready for use:

Example 16	1+2
Volume (l)	2
Glucose (g/l)	25
Na^+ (mM)	132
Cl^- (mM)	96
Lactate (mM)	40
Mg^{2+} (mM)	0,25
Ca^{2+} (mM)	1,75

Example 17	1+2
Volume (l)	2
Glucose (g/l)	25
Na^+ (mM)	132
Cl^- (mM)	96
Lactate (mM)	40
Mg^{2+} (mM)	0,25
Ca^{2+} (mM)	1,75

Example 18	1+2
Volume (l)	2
Glucose (g/l)	25
Na^+ (mM)	132
Cl^- (mM)	96
Lactate (mM)	40
Mg^{2+} (mM)	0,25
Ca^{2+} (mM)	1,75

5

Example 19-21

Two-compartment bag with acetate + bicarbonate

Compartment 1 (first single solution):

	Example 19	Example 20	Example 21
Volume (l)	0,100	0,100	0,100
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 2 (second single solution):

	Example 19	Example 20	Example 21
Volume (l)	1,9	1,9	1,9
Na^+ (mM)	134,1	134,1	134,1
Cl^- (mM)	91,4	91,4	91,4
Bicarbonate (mM)	12,11	12,11	12,11
Acetate (mM)	30,0	30,0	30,0
Mg^{2+} (mM)	0,26	0,26	0,26
Ca^{2+} (mM)	1,84	1,84	1,84

Solution, mixed and ready for use:

Example 19	1+3
Volume (l)	1,9
Glucose (g/l)	25
Na^+ (mM)	132
Cl^- (mM)	96
Bicarbonate (mM)	11,5
Acetate (mM)	28,5
Mg^{2+} (mM)	1,75
Ca^{2+} (mM)	0,25

Example 20	1+3
Volume (l)	1,9
Glucose (g/l)	25
Na^+ (mM)	132
Cl^- (mM)	96
Bicarbonate (mM)	11,5
Acetate (mM)	28,5
Mg^{2+} (mM)	1,75
Ca^{2+} (mM)	0,25

Example 21	1+3
Volume (l)	1,9
Glucose (g/l)	25
Na^+ (mM)	132
Cl^- (mM)	96
Bicarbonate (mM)	11,5
Acetate (mM)	28,5
Mg^{2+} (mM)	1,75
Ca^{2+} (mM)	0,25

Example 22-24

Three-compartment bag with lactate + bicarbonate, equal volumes glucose concentrate

Compartment 1 (first single solution):

	Example 22	Example 23	Example 24
Volume (l)	0,103	0,103	0,103
Glucose (g/l)	300	300	300
Na^+ (mM)	55,4	55,4	55,4
Cl^- (mM)	55,4	55,4	55,4
pH	1,8	2,1	2,5

Compartment 2 (third single solution):

	Example 22	Example 23	Example 24
Volume (l)	0,103	0,103	0,103
Glucose (g/l)	500	500	500
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	92,06	92,06	92,06
pH	1,8	2,1	2,5

Compartment 3 (second single solution):

	Example 22	Example 23	Example 24
Volume (l)	1,96	1,96	1,96
Na^+ (mM)	92,06	92,06	92,06
Cl^- (mM)	54,2	54,2	54,2
Lactate (mM)	30,0	30,0	30,0
Bicarbonate (mM)	12,11	12,11	12,11
Mg^{2+} (mM)	0,27	0,27	0,27
Ca^{2+} (mM)	1,84	1,84	1,84

Solution, mixed and ready for use:

Example 22	1+3	2+3	1+2+3
Volume (l)	2,063	2,063	2,166
Glucose (g/l)	14,99	24,96	38,04
Na^+ (mM)	90,23	92,06	90,36
Cl^- (mM)	54,2	56,1	56,0
Lactate (mM)	29,1	28,5	27,7
Bicarbonate (mM)	11,7	11,5	11,2
Mg^{2+} (mM)	0,25	0,25	0,24
Ca^{2+} (mM)	1,75	1,75	1,74

Example 23	1+3	2+3	1+2+3
Volume (l)	2,063	2,063	2,166
Glucose (g/l)	14,99	24,96	38,04
Na^+ (mM)	90,23	92,06	90,36
Cl^- (mM)	54,2	56,1	56,0
Lactate (mM)	29,1	28,5	27,7
Bicarbonate (mM)	11,7	11,5	11,2
Mg^{2+} (mM)	0,25	0,25	0,24
Ca^{2+} (mM)	1,75	1,75	1,74

Example 24	1+3	2+3	1+2+3
Volume (l)	2,063	2,063	2,166
Glucose (g/l)	14,99	24,96	38,04
Na^+ (mM)	90,23	92,06	90,36
Cl^- (mM)	54,2	56,1	56,0
Lactate (mM)	29,1	28,5	27,7
Bicarbonate (mM)	11,7	11,5	11,2
Mg^{2+} (mM)	0,25	0,25	0,24
Ca^{2+} (mM)	1,75	1,75	1,74

Example 25-28

Four-compartment bags, containing bicarbonate:

Compartment 1 (second single solution):

	Example 25	Example 26	Example 27	Example 28
$NaHCO_3$	95,5 mM	112 mM	139 mM	133 mM
Na_2CO_3	304,5 mM	258 mM	661 mM	607 mM
pH	10,3	10,3	10,3	10,3
Volume	0,196 l	0,196 l	0,098 l	0,098 l

Compartment 2 (additional single solution):

	Example 25	Example 26	Example 27	Example 28
HCl	38,74 mM	38,74 mM	39,19 mM	39,19 mM
NaCl	78,88 mM	78,88 mM	71,94 mM	71,94 mM
$CaCl_2*2H_2O$	1,99 mM	1,99 mM	1,88 mM	1,88 mM
$MgCl_2*6\ H_2O$	0,57 mM	0,57 mM	0,54 mM	0,54 mM
Lactate	-	3,41 mM	-	3,22 mM
pH	1,3	1,3	1,3	1,3
Volume	1,764 l	1,764 l	1,862 l	1,862 l

Compartment 3 (first single solution):

	Example 25	Example 26	Example 27	Example 28
Glucose	500 g/l	500 g/l mM	500 g/lmM	500 g/l
pH	2,0	2,0	2,0	2,0
Volume	0,062 l	0,062 l	0,062 l	0,062 l

Compartment 4 (third single solution):

	Example 25	Example 26	Example 27	Example 28
Glucose	500 g/l	500 g/l mM	500 g/lmM	500 g/l
pH	2-2,6	2-2,6	2-2,6	2-2,6
Volume	0,103 l	0,103 l	0,103 l	0,103 l

Solution, mixed and ready for use:

Example 25	Comparment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl^-	107,8 mM	105,6 mM	102,5 mM
Na^+	137,1 mM	134,4 mM	130,5 mM
Ca^+	1,74 mM	1,70 mM	1,65 mM
Mg^+	0,50 mM	0,49 mM	0,47 mM
HCO_3^-	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

Example 26	Comparment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl^-	107,8 mM	105,6 mM	102,5 mM
Na^+	135,6 mM	132,9 mM	129,1 mM
Ca^+	1,74 mM	1,70 mM	1,65 mM
Mg^+	0,50 mM	0,49 mM	0,47 mM
HCO_3^-	35,9 mM	35,2 mM	34,1 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,98 mM	2,92 mM	2,83 mM

5

Example 27	Comparment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl^-	113,2 mM	110,9mM	107,7 mM
Na^+	137,1 mM	134,3 mM	130,5 mM
Ca^+	1,73 mM	1,70 mM	1,65 mM
Mg^+	0,50 mM	0,49 mM	0,47 mM
HCO_3^-	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l

Example 28	Comparment 1+2+3	Compartment 1+2+4	Compartment 1+2+3+4
Volume	2,022 l	2,063 l	2,125 l
pH	7,0	7,0	7,0
Cl^-	113,2 mM	110,9mM	107,7 mM
Na^+	137,5 mM	134,7 mM	130,8 mM
Ca^+	1,73 mM	1,70 mM	1,65 mM
Mg^+	0,5 mM	0,49 mM	0,47 mM
HCO_3^-	38,8 mM	38,0 mM	36,9 mM
Glucose	15,3 g/l	25,0 g/l	38,8 g/l
Lactate	2,97 mM	2,91 mM	2,82 mM

In summary, based on the above results, the inventors concluded that a highly biocompatible medical solution containing glucose and/or glucose-like compounds can be prepared, provided that the solution containing glucose and/or glucose-like compounds has a pH within the range of 1.8-2.6.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

1. A medical solution comprising a first single solution containing glucose and/or glucose-like compound, wherein said first single solution has a pH in the range of 1.8 - 2.6.

2. The medical solution according to claim 1, wherein said first single solution has a pH in the range of 2.0 - 2.6.

3. The medical solution according to claim 1, wherein said first single solution has a pH in the range of 1.8 - 2.5.

4. The medical solution according to claim 1, wherein said first single solution has a pH in the range of 2.0 - 2.5.

5. The medical solution according to claim 1, wherein said first single solution has a pH in the range of 1.8 - 2.3.

6. The medical solution according to claim 1, wherein said first single solution has a pH in the range of 2.0 - 2.3.

7. The medical solution according to any of the previous claims, wherein the medical solution comprise a second single solution containing a buffer solution having such a pH and buffering capacity that when said first and second single solutions up on use are to be mixed to form a final solution, said final solution has a pH of 6.0 - 7.6.

8. The medical solution according to any of the previous claims, wherein the medical solution further contains one or more electrolytes.

9. The medical solution according to claim 8, wherein said electrolytes comprise one or more of the ions of sodium, calcium, potassium, magnesium and/or chloride.

10. The medical solution according to claim 8 or 9, wherein one or more electrolytes are arranged in said second single solution.

11. The medical solution according to any of claims 8-10, wherein one or more electrolytes are arranged in said first single solution.

12. The medical solution according to any of the previous claims, wherein the medical solution further comprises a third single solution and wherein said third single solution also contains glucose and/or glucose-like compounds and has a pH of at least 1.8, preferably at least 2.0 and a pH of at most 2.6, preferably at most 2.5, most preferably at most 2.3.

13. The medical solution according to claim 12, wherein one or more electrolytes are arranged in said third single solution.

14. A medical solution according to claim 12 or claim 13, wherein said first and third single solutions contain different total amounts of glucose and/or glucose-like compounds, wherein said first and third single solutions, up on use, individually or jointly is/are to be mixed with said second single solution to form a final solution, and wherein said final solution has a pH in the range of 6.0 - 7.6.

15. The medical solution according to any of claims 7 to 14, wherein the different single solutions are provided in different compartments in a multi-compartment bag before being mixed to the final solution.

16. A method for producing a medical solution according to any of the previous claims, said method comprising:

providing said first single solution and optional second and third single solutions in separate compartment(s), and thereafter

terminal sterilizing said single solution(s).

17. A method according to claim 16, wherein terminal sterilization is heat sterilization and/or radiation sterilization.

18. A method according to claim 16 or 17, wherein terminal sterilization is heat sterilization at a temperature of at least 100°C, preferably at least 121°C.

19. A method according to any of claims 16-18, wherein said first single solution and said second single solution, after terminal sterilization and up on use, are mixed to form a final solution.

20. A method according to any of claims 16-18, wherein said second single solution and said third single solution, after terminal sterilization and up on use, are mixed to form a final solution.

21. A method according to any of claims 16-18, wherein said first single solution, said third single solution and said second single solution, after terminal sterilization and up on use, are mixed to form a final solution.

22. A multi-compartment bag comprising the medical solution according to any of claims 1-15.

23. A use of a medical solution according to any of claims 1-15.

ABSTRACT

The present invention relates to a medical solution comprising a first single solution containing glucose and/or glucose-like compound. According to the present invention said first single solution has a pH in the range of 1.8-2.6. The present invention further relates to a method for producing said medical solution as well as use thereof.

NO 383-US01
1/6

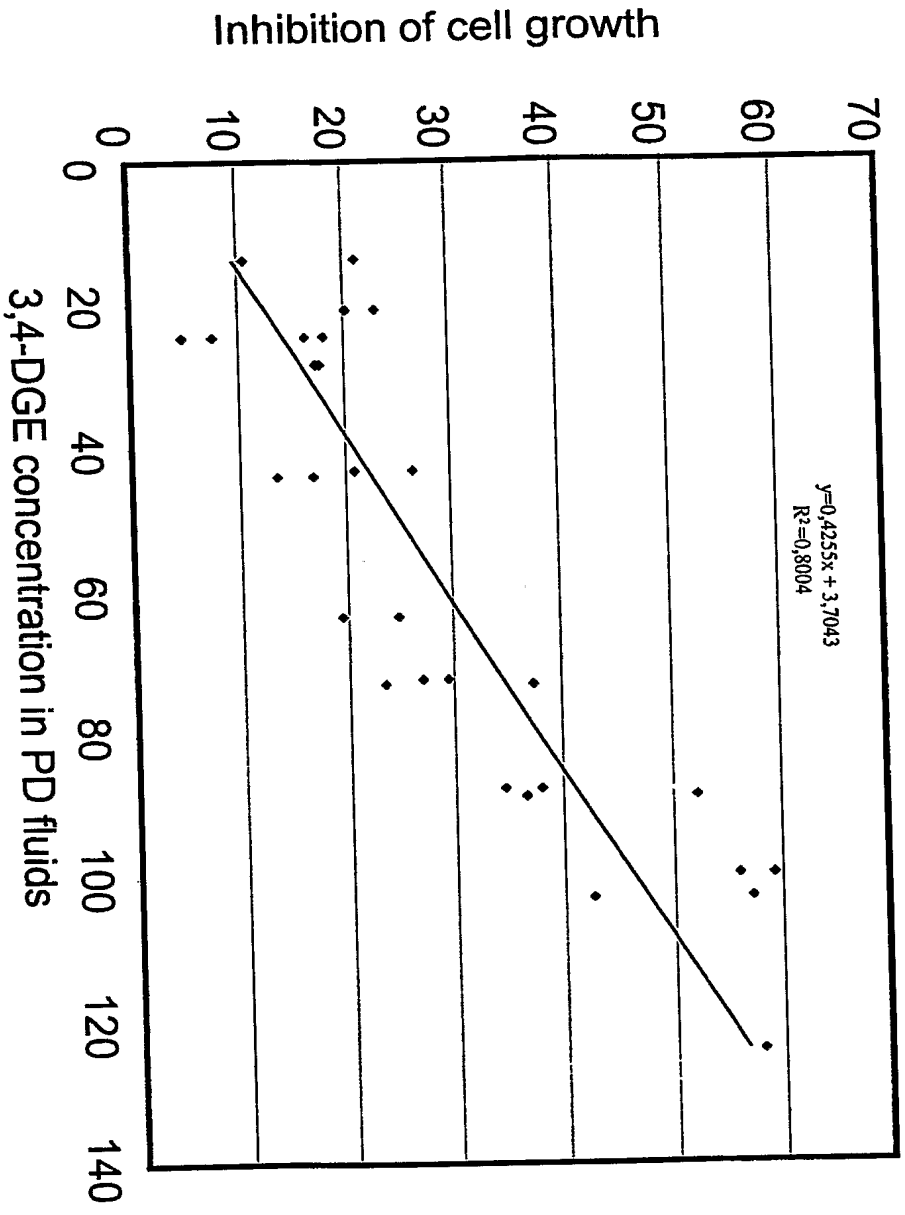


Fig. 1

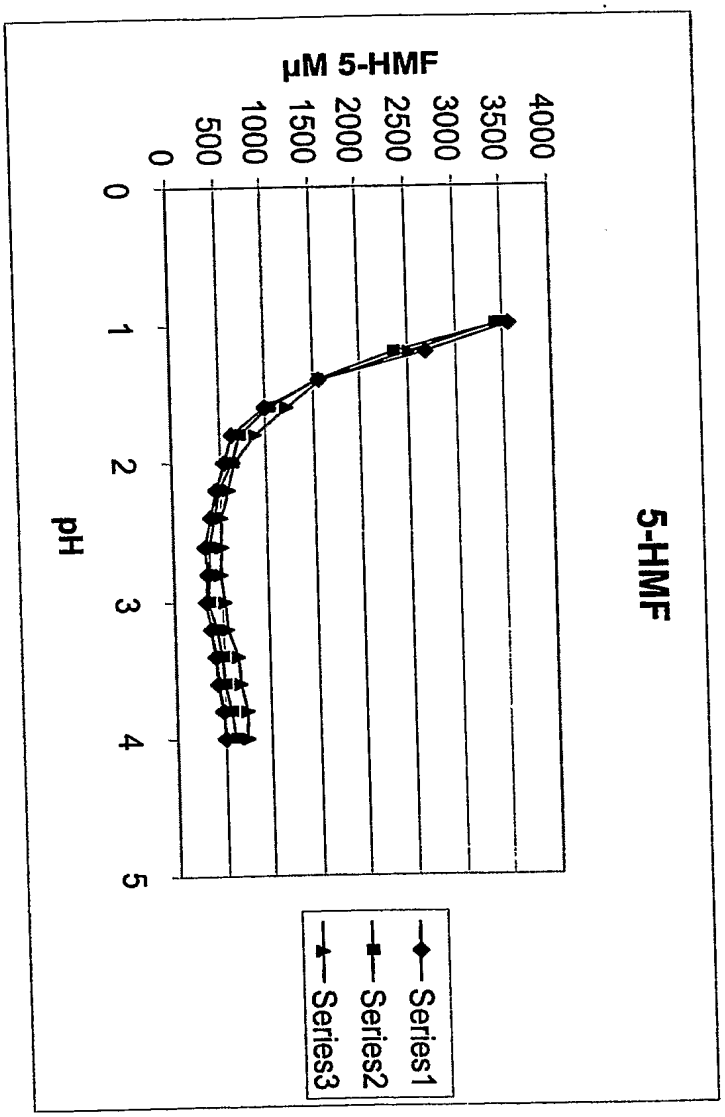


Fig. 2a

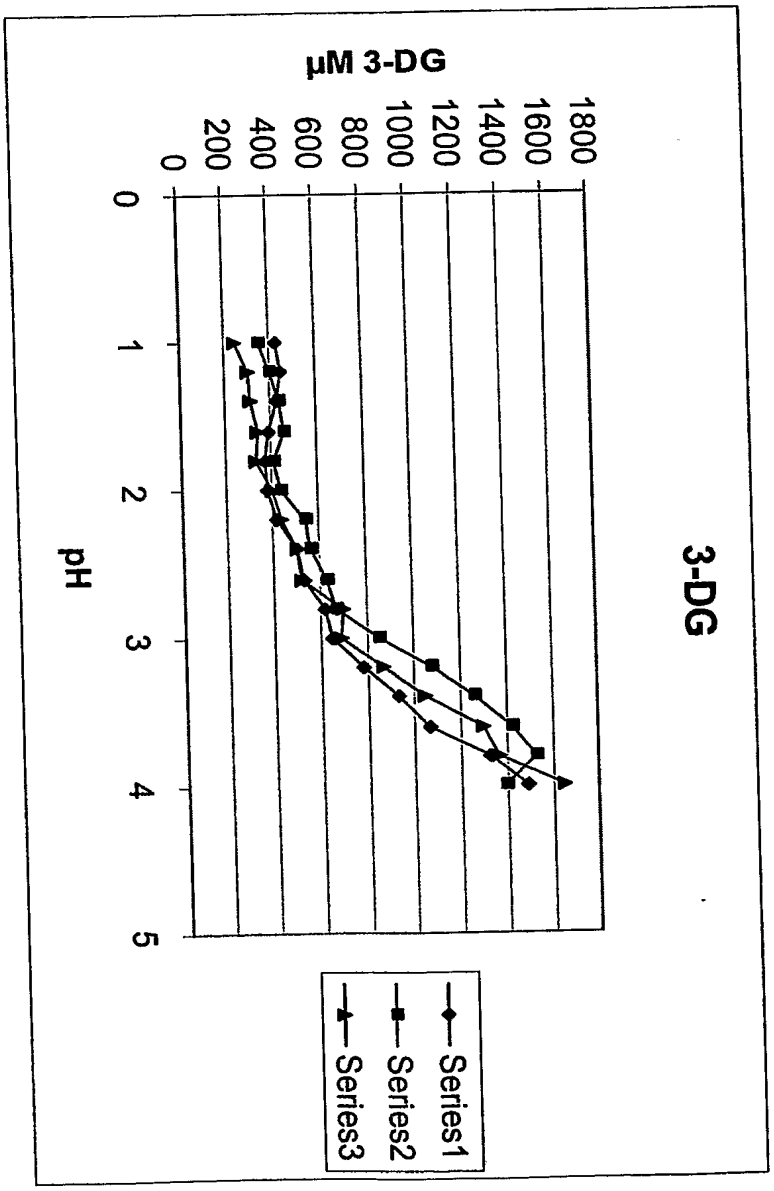


Fig. 2b

NO383-US01
4/6

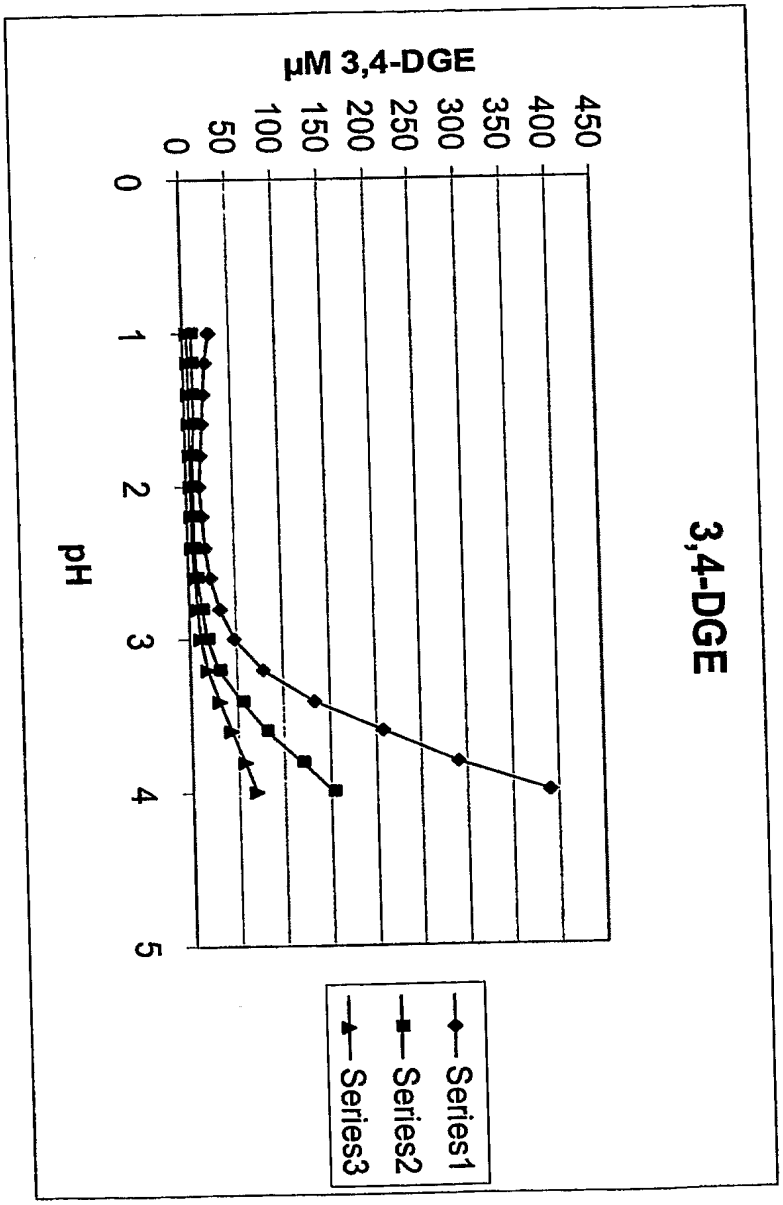


Fig. 2c

N0383-US01
5/6

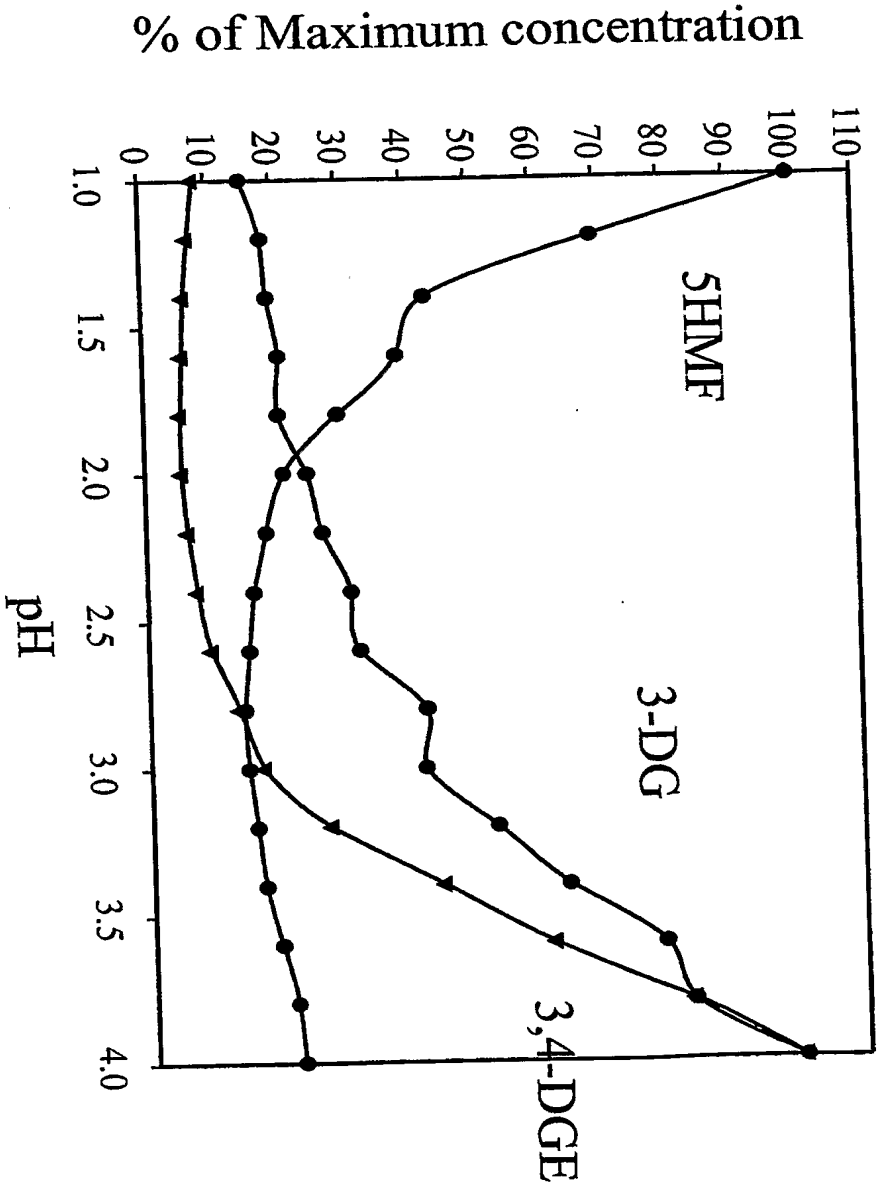


Fig. 3

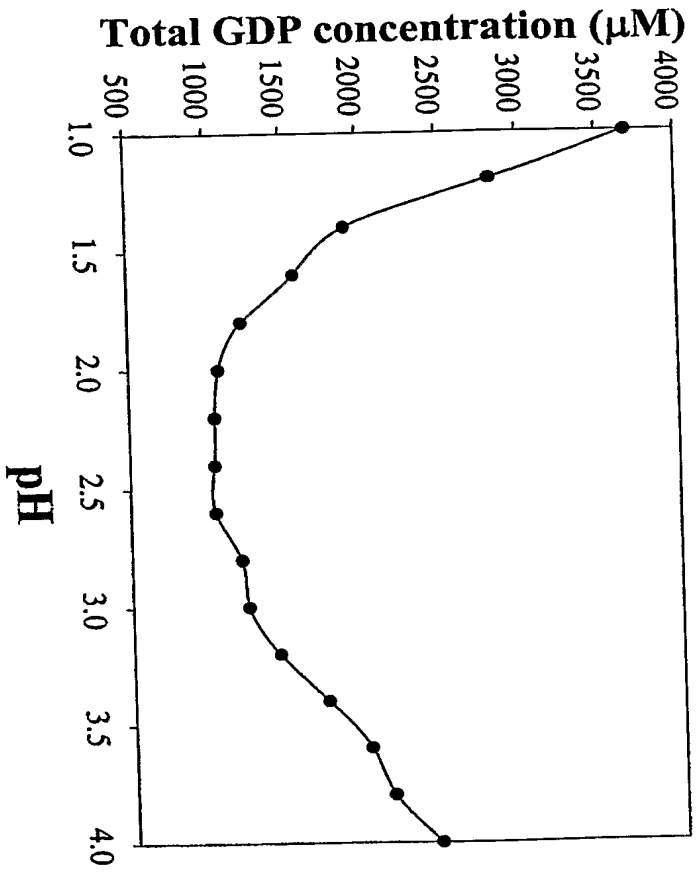


Fig. 4